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Martin G. Linihan

Name

Signature

September 28, 2004

Date of Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ross C. Terrell

Serial No. 10/644,500

Group Art Unit 1621

Filed: August 20, 2003

Examiner: M. Shippen

For: METHOD FOR THE PREPARATION OF SEVOFLURANE

BRIEF IN SUPPORT OF APPEAL

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Herewith is appellant's Brief on Appeal in triplicate together with deposit account authorization for payment of the appeal fee.

REAL PARTY IN INTEREST

Minrad Inc., owner by assignment of the above-identified application and the invention set forth therein, is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences related to this application.

STATUS OF CLAIMS

Applicant hereby appeals the Examiner's Final Rejection dated January 27, 2004 rejecting claims 1-13 and 18-24.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to the Final Rejection of January 27, 2004. The claims in their form as finally rejected by the Examiner are set forth in the attached Appendix.

SUMMARY OF THE INVENTION

The invention provides a method for the preparation of servoflurane which comprises (a) providing a liquid mixture of $(CF_3)_2CHOCH_2Cl$, hydrogen flouride, and an amine and (b) reacting the mixture, to form $(CF_3)_2CHOCH_2F$ (Page 5, lines 18-21).

Typically, the reaction is conducted by heating the mixture at a temperature in a range from about 40°C to about 80°C (Page 6, lines 6 and 7) for a period of time between about four to about twelve hours (Page 6, line 8).

The amine preferably is selected from a primary amine, a secondary amine or a tertiary amine (Page 6, lines 11 and 12). The amine can also be a cyclic amine (Page 6, lines 16 and 17).

The mixture can comprise $(CF_3)CHOCHCl_2$ (Page 6, line 19).

The yield of the reaction is at least 50 percent (Page 6, line 33).

The method of the invention advantageously does not use expensive reagents, such as elemental fluorine or bromine trifluoride, does not involve the use of high temperatures and pressures, and does not create large amounts of hazardous waste as a byproduct (Page 5, lines 12-15). Another advantage of the invention is that it allows both the monochloro- and dichloro-ethers to be present during the reaction (Page 8, lines 17 and 18). A further advantage is the simplicity and efficiency of the overall reaction (Page 8, lines 26-31).

ISSUE

Whether claims 1-13 and 18-24 patentably distinguish over Muffler (DE 2823969) in view of Regan (USP 3683092) under 35 USC 103.

Applicant wishes to remove the obvious-type double patenting rejection of claims 1-13 and 18-24 as an issue by agreeing to file a terminal disclaimer if claims 1-13 and 18-24 in their present form are determined by the Board to be allowable.

GROUPING OF CLAIMS

Claims 1-13 and 18-24 can be grouped together.

ARGUMENT

The rejection of claims 1-13 and 18-24 under 35 USC 103 based on Muffler (DE 2823969) in view of Regan (USP 3683092) is believed to be improper. Applicant notes the following arguments used by the Examiner in the Final Rejection.

"Such reactants differ only as to substituents that are removed from the reaction site and do not enter into the reaction. One would not expect the different substituents to affect the outcome of the reaction."

"Electronic and steric factors of the flourinated methyl groups would not have been expected to affect the outcome of the reaction. First, the reaction takes place at the chloro group which is removed from the flourinated methyl groups of the $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ reactant."

"One would not expect the electronic and steric factors of the flourinated methyl groups so removed to greatly influence the outcome of the reaction."

Basically the Examiner's argument appears to be that the CF_3 groups in the molecule $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ are "removed" from the reaction site, ie the CH_2Cl group. However, this argument is based on what the molecule looks like when written out on paper in two dimensions. One cannot, of course, predict interatomic distances etc, based on a flat two-dimensional representation since the molecule is three-dimensional. If one makes a three-dimensional molecule it is easily seen that the CF_3 groups are not as far removed from the reaction site as the Examiner proposes based on this inspection if the molecules are written out in two dimensions.

Notwithstanding all of this it is difficult to predict reactivity based on either two-dimensional or three-dimensional molecules. It is much better to base any predictions on actual experimental data if available. Fortunately, there are some experimental data available for the case at hand relative to whether or not the reaction of $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ could accurately be predicted from the prior art.

The Muffler patent states the following: "Any organic starting compound can be used for the procedure that is substituted on at least one position by nucleophilically substitutable chlorine." (emphasis added). U.S. Patent 4,874,901 (attached hereto as Exhibit A) includes three examples, which are covered by these definitions. These are the following:

1. $\text{CF}_3\text{CHClOCHF}_2 + \text{KF} \rightarrow \text{CF}_3\text{CHFOCHF}_2$
2. $(\text{CF}_3)_2\text{CHOCHCl}_2 + \text{NaF} \rightarrow (\text{CF}_3)_2\text{CHOCHF}_2$
3. $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl} + \text{KF} \rightarrow (\text{CF}_3)_2\text{CHOCHF}_2$

In all three of these examples the chlorine is "nucleophilically" substituted it is well known that these NaF and KF reactions are nucleophilic reactions. Therefore, based on the statement in the Muffler patent, one would expect these reactions to work with hydrofluorides.

Now, if one uses the Examiner's argument that the reaction of $(\text{CF}_3)_2\text{CHOCHCl}_2$ is obvious then the other two reactions are also obvious. If these reactions do not proceed then the reaction is less obvious than the Examiner proposes. The chloroethers in examples 1 and 2, do not, in fact, react with amine hydrofluorides to give the expected products.

EXAMPLE 1

Reaction of $\text{CF}_3\text{CHClOCHF}_2$ with Triethyl amine Hydrofluoride

$\text{CF}_3\text{CHClOCHF}_2$ (46g, 0.25 mole) was mixed with $(\text{Et})_3\text{N} \cdot 3\text{HF}$ (0.1 mole) and $(\text{Et})_3\text{N}$ (0.2 mole). (Note: this is equivalent to 0.3 mole of $(\text{Et})_3\text{N} \cdot \text{HF}$). There was a small exotherm observed on mixing. The resulting clear solution was refluxed for 16 hours using a water-cooled reflux condenser, the exit of which was

connection to a "Dry Ice" trap in order to trap any $\text{CF}_3\text{CFOCHF}_2$ (b.p. 23°C) which might be formed. At the end of 16 hours, the reaction mixture was washed with water and dilute HCl and dried with K_2CO_3 . 44g of product was recovered which was analyzed by gas chromatography using a 15' x 1/8" 20% carbowax 20m on 8100 mesh chromsorb WHP column at 60°C . The product was 99.92% starting ether $\text{CF}_3\text{CHClOCHF}_2$. There was no $\text{CF}_3\text{CFHOCHF}_2$ collected in the "Dry Ice" trap. The fact that this ether does not react is very telling since it is structurally so closely related to one of the compounds in the Muffler patent $\text{CF}_3\text{CHClOCH}_3$.

EXAMPLE 2

Reaction of $(\text{CF}_3)_2\text{CH-OCHCl}_2$ with Triethyl amine Hydrofluoride

$(\text{CF}_3)_2\text{CHOCHCl}_2$ (11.7g 0.05 mole) was mixed with 3.2g $(\text{Et})_3\text{N} \cdot 3\text{HF}$ (3.2g, 0.02 mole) and $(\text{Et})_3\text{N}$ (4g, 0.04 mole). (This makes 0.06 mole of $(\text{Et})_3\text{N} \cdot \text{HF}$) to give a clear solution with a very small amount of ppt. This solution was heated at 60°C for eight hours. There was no precipitate of $(\text{Et})_3\text{N} \cdot \text{HCl}$ formed. The product was washed with water and dilute HCl and dried with K_2CO_3 to give 8g of product. This product was analyzed by gas chromatography using the same conditions as in Experiment #1. This product was essentially unchanged starting material $(\text{CF}_3)_2\text{CH-OCHCl}_2$ (95%).

Thus, there are experimental data relative to three reactions all of which should work based on the criteria outlined in the Muffler patent and the U.S. Patent. However, only one of the three does work. If two out of three reactions, which should work, do not, how can one say that the reaction is obvious?

It would appear reasonable to suggest, based on the Muffler patent and the U.S. Patent, that the reaction of $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ with amine hydrofluorides be tried. However, it does not appear reasonable to predict with certainty that the reaction would work. There is ample precedent in the law that a mere suggestion to try is not enough to render claims unpatentable. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 5 USPQ2d (Fed. Civ. 1998, *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987), *N.V. Alczo v. EI. duPont de Nemours & Co.*, 1 USPQ2d 1081 (Fed. Cir. 1987), *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986) and *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 220 USPQ97 (Fed. Civ. 1983). It appears that here we have at best only a suggestion to try rather than a definite prediction that the reaction is obvious.

A number of decisions find nonobviousness and patentability because of uncertainty in the art or the absence of a reasonable probability of success. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). *Ortho Pharmaceutical Corp. v. Smith*, 22 USPQ2d 1119 (Fed. Cir. 1992). *Merck & Co. v. Danbury Pharmacal Inc.*, 8 USPQ2d 1793 (D. Del. 1988). In this regard, the Federal Circuit has noted:

"Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . Both the suggestion and the reasonable

expectation of success must be founded in the prior art, not in the applicant's disclosure."

In re Vaeck, 20 USPQ 1442 (Fed. Cir. 1991).

Regan does not disclose anything considered to have a bearing on the reasons why claims 1-13 and 18-24 are believed to be nonobvious and thus patentable over Muffler. Regan describes the synthesis of sevoflurane in which $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ is reacted with potassium fluoride. Regan also states that the reaction of antimony trifluoride with $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ does not produce sevoflurane ($(\text{CF}_3)_2\text{CHOCH}_2\text{F}$). Column 3, lines 1 to 10. This occurs despite the usefulness of antimony trifluoride in preparing $(\text{CF}_3)_2\text{CHOCHF}_2$ and $(\text{CF}_3)_2\text{CHOCHFCl}$ from the corresponding chlorinated ethers. Thus, Regan teaches the unpredictable results obtained by switching from one fluorinating agent to another.

In view of the foregoing, claims 1-13 and 18-24 are believed to patentably distinguish over Muffler and Regan within the meaning of 35 USC 103.

CONCLUSION

The Board is respectfully requested to reverse the 35 USC 103 rejection of record, for the reasons set forth above, and find that claims 1-13 and 18-24 define patentable subject matter over the art of record.

Respectfully submitted,

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APPENDIX

CLAIMS ON APPEAL

4. A method for the preparation of sevoflurane which comprises:

- (a) providing a liquid mixture of $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$, hydrogen fluoride, and an amine; and
- (b) reacting the mixture; to form $(\text{CF}_3)_2\text{CHOCH}_2\text{F}$.

5. The method of claim 1, wherein the mixture is reacted by heating.

6. The method of claim 1, wherein the mixture is reacted by heating at 40°C to 80°C.

7. The method of claim 1, wherein the mixture is reacted by heating at 55°C to 65°C.

8. The method of claim 1, wherein the amine is selected from a primary amine, a secondary amine, or a tertiary amine.

9. The method of claim 5, wherein the amine is selected from propylamine or diethylamine.

10. The method of claim 5, wherein the amine is a tertiary amine.

11. The method of claim 7, wherein the tertiary amine is a trialkylamine.

12. The method of claim 8, wherein the trialkylamine is selected from triethylamine, tripropylamine, triisopropylamine, tributylamine, dimethyl ethyl amine, di-isopropyl ethyl amine, or mixtures thereof.

13. The method of claim 1, wherein the amine is a cyclic amine.

14. The method of claim 10, wherein the cyclic amine is selected from pyrrolidine, N-methyl pyrrolidine, or piperidine.

15. The method of claim 1, wherein the mixture comprises $(\text{CF}_3)_2\text{CHOCHCl}_2$.

16. The method of claim 12, wherein the mixture comprises from 0.01 to 20 percent by weight of $(\text{CF}_3)_2\text{CHOCHCl}_2$.

18. The method of claim 1, wherein the mole ratio of the $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ to the hydrogen fluoride is from 1:1 to 1:2.

19. The method of claim 1, wherein the mole ratio of the $(\text{CF}_3)_2\text{CHOCH}_2\text{Cl}$ to the amine is from 1:0.3 to 1:2.

20. The method of claim 3, wherein the mixture is reacted for 4 to 12 hours.

21. The method of claim 3, wherein the mixture is reacted for 4 to 10 hours.

22. The method of claim 3, wherein the mixture is reacted for 4 to 7 hours.

23. The method of claim 1, wherein the yield of the reaction is at least 50 percent.

24. The method of claim 1, wherein the yield of the reaction is at least 65 percent.